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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,916	02/19/2002	Steen Klysner	3631-0112P	3837

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,916	KLYSNER, STEEN	
	Examiner	Art Unit	
	Bruce D. Hissong	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *73-75,77-80 85-87,89-94,100, and 133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *73-75,77-80,85-87,89-94,100 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S-D-D

DETAILED ACTION

Response to Applicant's Amendment

A. Formal Matters

1. The amendment filed on 6/15/2005 has been made of record.

2. Claims 69-94, 100, and 133-141 were pending. Claims 69-72, 76, 81-84, 88, and 134-141 were cancelled in the amendment filed on 6/15/2005. Therefore, claims 73-75, 77-80, 85-87, 89-94, 100, and 133 are currently pending and are considered for examination.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 12/15/2004.

B. Information Disclosure Statement

The information disclosure submitted on 6/15/2005 has been made of record and has been fully considered. The Examiner has noted that year of publication is missing for several documents listed on p. 11 of the information disclosure statement submitted on 6/15/2005. The Examiner has listed two of the references (Mori *et al*, and Lee *et al*) on USPTO Form 892. However, the Examiner was unable to find the references for Ortega *et al*, and Karlin *et al*. It is incumbent upon the Applicant to provide full references for the indicated documents.

C. Specification

Objection to the specification on the basis of improperly indicated trademarks is withdrawn in response to the Applicant's amendments.

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D. 35 USC § 112, first paragraph – written description

1. Rejection of claims 73-75, 77-80, 85-87, 89-94, 100, and 133 under 35 USC § 112, first paragraph, regarding lack of written description, "foreign T_H epitopes" and "foreign T-cell epitope is promiscuous", as set forth on page 5 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's arguments.

2. Rejection of claims 73-75 under 35 USC § 112, first paragraph, regarding lack of written description for methods "which effects targeting" and "which stimulates the immune system", methods drawn to using "a binding partner of an APC specific surface antigen", and a third moiety of "lipid nature", as set forth on pages 6-7 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's cancellation of this term from the claims.

3. Rejection of claims 73-75, 77-80, 85-87, 89-91, 93-94, 100, and 133 under 35 USC § 112, first paragraph, regarding lack of written description for methods using a "subsequence", as set forth on pages 5-6 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's cancellation of this term from the claims.

4. Claim 92 remains rejected under 35 USC § 112, first paragraph for lack of written description regarding a "subsequence", as set forth in a prior Office Action mailed on 12/15/2004. The specification defines "subsequence" as "any conservative stretch of at least 3 amino acids or, when relevant, of at least 3 nucleotides....." This definition does not limit the composition and structure of the subsequence, which can essentially be any amino acid, or stretch of amino acids, the identities of which are not stated in the specification. Furthermore, the Applicant's

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amendment does not further define or limit the term "subsequence", and provides no written description of the structural and/or functional characteristics of the claimed "subsequence".

5. Claims 73-75, 77-80, 85-87, 89-94, 100, and 133 remain rejected under 35 USC § 112, first paragraph, regarding lack of written description for methods of using "analogues" of IL-5, as set forth on page 5 of the prior Office Action mailed on 12/15/2004. The Applicants argue that "analogue" is defined by amended claim 133, in that an IL-5 "analogue" must posses the following characteristics: (1) it must include a *substantial* fraction of IL-5 B-cell epitopes, and therefore be cross-reactive with wild-type IL-5; (2) it must include *at least* one foreign T_H epitope; and (3) it must be capable of inducing antibodies that cross-react with wild-type IL-5. The Applicants assert that this definition fulfills both 35 U.S.C. 112, first paragraph, and USPTO guidelines for written description. These arguments have been fully considered and are not found to be persuasive because this definition still does not limit the term "analogue" in a structural sense. The specification does not define what constitutes a "substantial" number of B-cell epitopes, nor is it limiting for the number of possible B-cell and foreign T_H epitopes. Thus, "analogue" is not fully described in a structural sense in a way that a person of ordinary skill in the art would be able to conceive.

6. Claims 73-75 and 77-80 remain rejected under 35 USC § 112, first paragraph for lack of written description regarding methods including "at least one modification", "results in the provision of a fusion polypeptide", and "substitution and/or deletion and/or insertion and/or addition", as set forth on page 6 of the prior Office Action mailed on 12/15/2004. The Applicant argues that amended claim 133 defines the modifications as those that preserve "a substantial fraction of IL-5 B cell epitopes". The Applicant's arguments have been fully considered and are

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not deemed persuasive because the exact nature of the modification(s) is not clear and is not defined in either the claims or the specification. Specifically, the number of, and the exact nature of the modifications (substitution or deletion or insertion or addition) must be unambiguously stated. Furthermore, what constitutes a "substantial" fraction of B cell epitopes is not defined in a structural or quantitative sense.

7. Claim 85 remains rejected under 35 USC § 112, first paragraph, for lack of written description regarding methods using IL-5 with specified locations for modifications, as set forth on page 7 of the prior Office Action mailed on 12/15/2004. Claim 85 has been amended to read on an IL-5 polypeptide that has been modified "to introduce the foreign T_H epitope in at least one of loops 1-3 or in the amino acid residues C-terminal to helix D, said helix D corresponding to those shown in Fig. 3 for human and murine IL5". The Applicants argue that this amendment does indeed provide description of both structure and function by limiting the type of modification to that of introduction of a foreign T_H epitope. The Applicant's arguments have been fully considered and are not deemed persuasive. Amended claim 85 reads on an IL-5 polypeptide that is modified to introduce the foreign T_H epitope in *at least* one of *several* locations within the IL-5 polypeptide, and while it does limit the type of modification, it does not limit the *exact number* or *exact location(s)* of the modifications.

E. 35 USC § 112, first paragraph – enablement

1. Rejection of claims 73-75, 77-80, 89-94, 100, and 133 under 35 USC § 112, first paragraph, regarding lack of enablement for "foreign T_H epitopes" and "foreign T-cell epitope is promiscuous", as set forth on pages 10-11 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's arguments.

2. Rejection of claims 73-75, under 35 USC § 112, first paragraph, regarding lack of enablement for methods "which effects targeting" and "which stimulates the immune system", methods drawn to using "a binding partner of an APC specific surface antigen", and a third moiety of "lipid nature", as set forth on page 14 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's cancellation of the terms from the claims.

3. Rejection of claims 73-75, 77-80, 89-91, 93-94, 100, and 133 under 35 USC § 112, first paragraph, regarding lack of enablement for methods using a "subsequence", as set forth on pages 11-12 of the prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's cancellation of this term from the claims.

4. Rejection of claims 73-75, 77-80, 85-87, 89-94, 100, and 133 under 35 USC § 112, first paragraph, for lack of enablement regarding an "immunogenically effective amount", as set forth in a prior Office Action mailed on 12/15/2004, is withdrawn in response to Applicant's arguments.

5. Claim 92 remains rejected under 35 USC § 112, first paragraph for lack enablement regarding a "subsequence", as set forth ion pages 11-12 of the prior Office Action mailed on 12/15/2004. The Applicant's amendment filed on 6/15/2005 does not further address the "subsequence" of claim 92. Because neither the claims nor the specification disclose direction, guidance, or working examples of how to use the claimed "subsequence", or even what exactly the "subsequence" is, and due to the unpredictability associated with this art and the excessive

breath of the claim, a person of ordinary skill in the art would not know how to use the claimed "subsequence".

6. Claims 73-75, 77-80, 85-87, 89-94, 100, and 133 remain rejected under 35 USC § 112, first paragraph, regarding lack of enablement for methods of using "analogues" of IL-5, as set forth on page 5 of the prior Office Action mailed on 12/15/2004. The Applicants argue that "analogue" is defined by amended claim 133, in that an IL-5 "analogue" must posses the following characteristics: (1) it must include a *substantial* fraction of IL-5 B-cell epitopes, and therefore be cross-reactive with wild-type IL-5; (2) it must include *at least* one foreign T_H epitopes; and (3) it must be capable of inducing antibodies that cross-react with wild-type IL-5. The Applicants assert that this definition, and the teachings of the specification, are indeed enabling to a person of ordinary skill in the art. These arguments have been fully considered and are not found to be persuasive. As stated above, the specification does not define what constitutes a "substantial" number of B-cell epitopes, nor is it limiting for the number of possible B-cell epitopes. The claim is also not limiting for the number of T_H epitopes. It would require undue experimentation of the part of a person of ordinary skill in the art to determine how many B-cell epitopes are substantial enough to preserve cross-reactivity with autologous IL-5. Furthermore, it would also require undue experimentation to determine the number of foreign T_H epitopes required to break self-tolerance. Therefore, because the specification does not teach the exact number of both B-cell and foreign T_H epitopes, and as discussed below, the exact locations of the T_H epitopes within the B-cell epitopes, a person of ordinary skill in the art would not be able to use the claimed invention.

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7. Claims 73-75, 77-80, 85-87, 89-94, 100, and 133 remain rejected under 35 USC § 112, first paragraph for lack of enablement regarding methods of downregulating IL-5 using IL-5 with unlimited modifications, as set forth on pages 8-9 of the prior Office Action mailed on 12/15/2004. The Applicant argues that amended claim 133 defines the modifications as those that preserve "a substantial fraction of IL-5 B cell epitopes". The Applicant's arguments have been fully considered and are not deemed persuasive. The exact nature of the modification(s) is not clear and is not defined in either the claims or the specification. Specifically, the number of and the nature of the modifications (substitution or deletion or insertion or addition) are not unambiguously stated. A person of ordinary skill in the art would not know how to use the claimed invention due to the non-limiting language of the claims. Because of the breath of the claims, unpredictability, and the lack of direction or guidance disclosed in the specification, the claims are not enabling for methods of using IL-5 with unlimited modifications.

8. Claim 85 remains rejected under 35 USC § 112, first paragraph, for enablement regarding methods using IL-5 with specified locations for modifications, as set forth on pages 12-13 of the prior Office Action mailed on 12/15/2004. Amended claim 85 reads on an IL-5 polypeptide that has been modified "to introduce the foreign T_H epitope in at least one of loops 1-3 or in the amino acid residues C-terminal to helix D, said helix D corresponding to those shown in Fig. 3 for human and murine IL5". The Applicants argue that this amendment to claim 85 obviates the rejection in regard to enablement because it describes the type of modification. This argument has been fully considered and is not deemed persuasive because the amended claim is not enabling in regard to the exact number or exact location(s) of the modifications. Therefore, the claim is excessively broad, and due to the unpredictability of the art, and the lack of guidance or

direction from the specification, a person of ordinary skill in the art would not know how to use the claimed invention.

9. Claim 100 remains rejected under 35 USC § 112, first paragraph, for lack of enablement regarding "a method for treating asthma or other chronic allergic conditions characterized by eosinophilia", as set forth on page 13 of the prior Office Action mailed on 12/15/2004. The Applicant argues amending the claim to remove "preventing and/or ameliorating" obviates the rejection for enablement. The Applicant's argument has been fully considered and is not deemed persuasive. The breath of the claim encompasses many potential diseases that are characterized by eosinophila, and the claim and specification do not disclose other conditions characterized by eosinophila that would be expected to be responsive to downregulation of IL-5. Furthermore, the language of the specification or the claim does not define "treating". Due to the lack of guidance and examples in the specification, and the unpredictability of the art, a person of ordinary skill in the art would not know how to use the claimed invention without undue experimentation.

F. 35 USC § 112, second paragraph

1. All rejections under 35 USC § 112, second paragraph, have been withdrawn in response to Applicant's cancellation of relevant claims. The Examiner notes that claim 74 was inadvertently included in claims rejected under 35 USC § 112, second paragraph, as set forth on page 16 of the prior Office Action mailed on 12/15/2004.

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G. 35 USC § 103

1. Claims 73-75, 77-80, 85-87, 89-94, 100, and 133 remain rejected under 35 USC § 103 for obviousness under a combination of Dalum *et al,* in view of Steinaa *et al,* and further in view Foster *et al*, as set forth on pages 17-18 of the Prior Office action mailed on 12/15/04. The Applicants argue that any rejection based on Steinaa *et al* is improper because the reference is not properly prior art to the present application because Steinaa *et al* is assigned to the assignee of the present application. The Applicant's arguments have been fully considered and are not deemed persuasive. The fact that the reference and the application have the same assignee is not, by itself, sufficient evidence to disqualify the prior art under U.S.C. 103(c). The burden of establishing that subject matter is disqualified as prior art is placed on the applicant once the examiner has established a prima facie case of obviousness based on the subject matter. The Applicants must submit a statement that the common ownership was "at the time the invention was made" (see MPEP 706.02 (l)(2)).

2. Claims 73-75, 77-80, 85-87, 89-94, 100, and 133 remain rejected under 35 USC § 103 for obviousness under a combination of Dalum *et al,* in view of Mouritsen *et al,* and further in view of Foster *et al,* as set forth on pages 18-19 of the prior Office Action mailed on 12/15/2004. Dalum *et al* states that autotolerance to self-proteins can be overcome by introducing a T_H epitope(s) into self-proteins, but does not specifically describe downregulation of IL-5. Mouritsen *et al* describes a method of vaccination of self-proteins by recombinantly introducing foreign T_H epitopes into self-proteins, such as tumor necrosis factor and several interleukins. The Applicants argue in their response to the prior Office Action mailed on 12/15/2004 that it would not have been obvious to combine the teachings of Dalum *et al* and Mouritsen *et al* to obtain the present invention because active vaccination against IL-5 had not previously been

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demonstrated. The Applicants urge that one skilled in the art would not have had a reasonable expectation of success at the time of the invention, because the activity of IL-5 as a B-cell differentiating factor would be required for any active vaccination. In other words, inhibition of IL-5 would prohibit any attempts at active vaccination against IL-5 because IL-5 is required for B-cell differentiation, and overcoming this technical limitation therefore represents a novel, patentable invention.

The Applicant's arguments have been fully considered and are not deemed persuasive. The Applicant's specification teaches on p. 6, lines 21-24, "IL-5-deficient mice ('knock-out' mice) have also been studied. These mice (C57BL/6) have no obvious signs of disease and are fertile. *The immunoglobulin levels and the specific antibody response to DNP-OVA were normal*" (Kopf et al, 1996). The specification also teaches on p. 76, lines 19-22, "*as shown in a study using IL-5 knock-out mice, the T-cell dependent antibody response against ovalbumin as well as cytotoxic T-cell development appeared normal* (Kopf *et al*, 1996)". Additionally, it is known in the art that administration of neutralizing anti-IL-5 antibodies in mice does not affect antibody levels (Sher et al, 1990, p 63, 2nd column, 2nd paragraph, and Table II on p. 64). Therefore, because antibody production can clearly occur in the absence of, or inhibition of IL-5, one skilled in the art would have a reasonable expectation of success by combining the teachings of Dalum *et al* with those of Mouritsen *et al*. Furthermore, Foster *et al* show that IL-5 knock-out mice exhibit decreased eosinophilia and airway inflammation in response to an aerosol challenge with a sensitizing antigen, firmly establishing a role for IL-5 in promoting eosinophilia and airway inflammation. Thus, the teachings of Foster *et al* would provide motivation to a person of ordinary skill in the art to inhibit IL-5 as a method of treating eosinophilia and airway inflammation. Additionally, a person of ordinary skill in the art would have the motivation, and a reasonable expectation of success, to combine the teachings of

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Dalum *et al* and Mouritsen *et al* to inhibit IL-5 by active vaccination with IL-5 analogs containing foreign T_H epitopes. Finally, Sher *et al* is not being used as new grounds of rejection, but to support the Examiner's position of what was well known in the art, and inherent at the time of the present invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Bruce D. Hissong, Ph.D.,** whose telephone number is **(571) 272-3324**. The examiner can normally be reached on 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Anthony Caputa, Ph.D.**, can be reached on **(571) 272-0829**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bruce D. Hissong
Art Unit 1646

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER

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